Ranolazine in Symptomatic Diabetic Patients Without Obstructive Coronary Artery Disease: Impact on Microvascular and Diastolic Function

ORIGINAL RESEARCH

Ranolazine in Symptomatic Diabetic Patients Without Obstructive Coronary Artery Disease: Impact on Microvascular and Diastolic Function

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***Background*—**Treatments for patients with myocardial ischemia in the absence of angiographic obstructive coronary artery disease are limited. In these patients, particularly those with diabetes mellitus, diffuse coronary atherosclerosis and microvascular dysfunction is a common phenotype and may be accompanied by diastolic dysfunction. Our primary aim was to determine whether ranolazine would quantitatively improve exercise-stimulated myocardial blood flow and cardiac function in symptomatic diabetic patients without obstructive coronary artery disease.

***Methods and Results*—**We conducted a double-blinded crossover trial with 1:1 random allocation to the order of ranolazine and placebo. At baseline and after each 4-week treatment arm, left ventricular myocardial blood flow and coronary flow reserve (CFR; primary end point) were measured at rest and after supine bicycle exercise using ^{13}N-ammonia myocardial perfusion positron emission tomography. Resting echocardiography was also performed. Multilevel mixed-effects linear regression was used to determine treatment effects. Thirty-five patients met criteria for inclusion. Ranolazine did not significantly alter rest or postexercise left ventricular myocardial blood flow or CFR. However, patients with lower baseline CFR were more likely to experience improvement in CFR with ranolazine (r=−0.401, P=0.02) than with placebo (r=−0.188, P=0.28). In addition, ranolazine was associated with an improvement in E/septal e′ (P=0.001) and E/lateral e′ (P=0.01).

***Conclusions*—**In symptomatic diabetic patients without obstructive coronary artery disease, ranolazine did not change exercise-stimulated myocardial blood flow or CFR but did modestly improve diastolic function. Patients with more severe baseline impairment in CFR may derive more benefit from ranolazine.

***Clinical Trial Registration*—**URL: http://www.clinicaltrials.gov. Unique identifier: NCT01754259. **(*J Am Heart Assoc*. 2017;6: e005027. DOI: 10.1161/JAHA.116.005027.)**

Key Words: diabetes mellitus • microvascular dysfunction • positron emission tomography • randomized controlled trial • ranolazine

Myocardial ischemia in the absence of angiographic obstructive coronary artery disease (CAD) poses a significant management challenge for patients and providers. This clinical scenario is frequently encountered in clinical practice,[1] particularly in women,[2] and is associated with increased risk of adverse cardiovascular events and disability.[3,4] Diffuse coronary atherosclerosis and microvascular dysfunction is a common phenotype in these patients and may be accompanied by diastolic dysfunction.[5] These associations are especially evident among high-risk cohorts,

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Accompanying Tables S1 through S3 are available at http://jaha.ahajournals.org/content/6/5/e005027/DC1/embed/inline-supplementary-material-1.pdf

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including patients with diabetes mellitus[6] and patients with chronic renal impairment.[7,8] In diabetics, diffuse coronary vascular dysfunction precedes overt atherosclerosis,[9] and the absence of traditionally defined myocardial ischemia does not necessarily correspond to lower risk.[10] Importantly, current treatment strategies for obstructive epicardial CAD, such as percutaneous angioplasty and stenting, are ineffective for diffuse CAD and microvascular dysfunction.

Ranolazine is a novel anti-anginal agent[11,12] that, under ischemic conditions, inhibits the late sodium current in cardiomyocytes and thereby decreases sodium and calcium overload. Excess intracellular calcium may impair myocyte relaxation and contribute to ventricular diastolic stiffness, which in turn affects myocardial contractility and perfusion.[13,14] Although ranolazine's mechanism of action is thought to be mediated in part by increased myocardial blood flow (MBF),[15] prior studies utilizing vasodilator stress protocols have shown conflicting data regarding this hypothesis[16,17] and no prior study has tested it with an exercise stress protocol.

Accordingly, we conducted a randomized, double-blind, placebo-controlled, 2-way crossover trial in symptomatic diabetic patients without obstructive CAD to test the hypothesis that treatment with ranolazine would quantitatively improve exercise-related MBF and cardiac function.

Methods

Study Design

The study was a randomized, double-blinded, crossover trial with 1:1 random allocation to the order of ranolazine and placebo. The washout period between treatment arms was 3 days, representing ≈10 times the terminal half-life of ranolazine (7 hours). Figure 1 shows the study flow chart. At each of the 3 study visits, patients underwent a blood draw, a 12-lead ECG, a standard resting transthoracic echocardiogram, and dynamic supine bicycle exercise stress-rest myocardial perfusion positron emission tomography (PET). Serum biomarkers included N-terminal pro-B-type natriuretic peptide and high-sensitivity C-reactive protein. For safety monitoring, plasma glucose, hemoglobin A1c, lipid panels, complete blood count, and renal and liver function panels were also obtained at each visit.

Patient Population

Brigham & Women's Hospital provider patient panels were screened to identify patients with diabetes mellitus, stable angina and/or exertional dyspnea, and exercise tolerance of at least 3 metabolic equivalents on a treadmill or bicycle exercise tolerance test. Patients with obstructive CAD

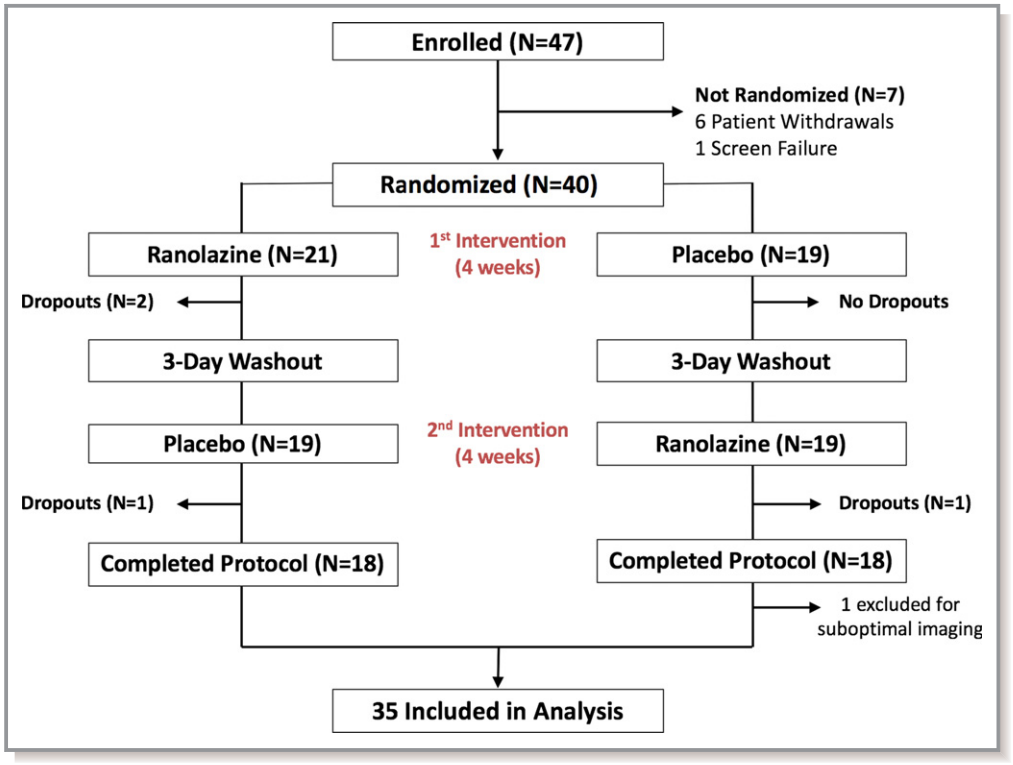

Figure 1. Patient enrollment, screening, randomization, and completion flow diagram.

(defined as ≥50% luminal stenosis) on clinically indicated invasive coronary angiography or coronary computed tomography (CT) angiography within 1 year prior to study screening were excluded, as were those with a history of cardiomyopathy (left ventricular ejection fraction <40%), moderate–severe valvular heart disease, uncontrolled hypertension (systolic blood pressure >180 mm Hg), renal impairment (estimated glomerular filtration rate <50 mL/min per 1.73 m^2), and/or a contraindication to ranolazine. Patients already taking ranolazine for clinical indications were also excluded. Qualifying patients were contacted by phone to request voluntary participation in the study. Consistent with prior ranolazine trials,[16,18,19] patient symptoms at baseline were confirmed using the Seattle Angina Questionnaire (ie, score <100)[20] and the Rose Dyspnea Scale (ie, score >0).[21] If patients had not undergone invasive or CT coronary angiography within 1 year, we performed screening coronary CT angiography and excluded any patients with ≥50% luminal stenosis from further study participation. The study was approved by the Partners Healthcare Institutional Review Board and registered at ClinicalTrials.gov (NCT 01754259). All study patients gave written informed consent.

Randomization

The order of ranolazine and placebo exposure was randomly assigned in a 1:1 ratio by the Investigational Drug Service at Brigham & Women's Hospital. During the 28-day treatment periods, ranolazine (Gilead Sciences, Foster City, CA) and matching placebo were administered as 500 mg by mouth twice daily for 1 week and increased to 1000 mg by mouth twice daily for 3 weeks, as tolerated. Minimum ranolazine dosing and duration of treatment periods were based on prior data that monotherapy with 500 mg twice daily for 1 week is sufficient to increase exercise tolerance in patients with chronic angina.[22] Treatment compliance was measured by pill count. Patients and study investigators were blinded to treatments and treatment order throughout the study protocol.

Assessment of Myocardial Blood Flow and Coronary Flow Reserve

MBF was measured at rest and in response to supine bicycle exercise using ^{13}N-ammonia as a flow tracer. Patients were studied using a whole body PET-CT scanner (Discovery RX or STE LightSpeed 64; GE Healthcare, Milwaukee, WI) after an overnight fast. Patients refrained from β-blockers, calcium channel blockers, and nitroglycerin for 24 hours before their scans. After transmission CT imaging and beginning with the intravenous bolus administration of ^{13}N-ammonia (≈15 mCi) at rest, list mode images were acquired for 20 minutes. After radioactive decay of the rest radioactive dose, the patient was positioned for supine bicycle exercise on the PET table, just outside the imaging gantry. Symptom-limited supine bicycle exercise stress using a standardized ramp protocol was then performed. At peak stress, exercise was stopped and patients were immediately repositioned in the PET gantry using skin landmarks, at which point a second dose of ^{13}N-ammonia (≈15 mCi) was administered followed by list mode imaging for 20 minutes. The time between peak exercise stress and ^{13}N-ammonia injection was ≈20 s. A second CT transmission scan was obtained immediately after completion of the stress imaging, and used for attenuation correction of the stress images. The average radiation exposure per complete PET/CT study was ≈2.8 mSv. Heart rate, blood pressure, and 12-lead ECG were recorded at baseline and every minute during and after exercise stress. An identical stress protocol and workload was used for stress PET scans after each treatment arm.

Assessment of the global extent and severity of regional perfusion abnormalities was assessed by quantifying the total perfusion deficit at rest, after stress, and their difference using commercially available software (QPS; Cedars Sinai, Los Angeles, CA). Patients with a total perfusion deficit during stress >8.8% (corresponding to a summed stress score >6 and suggestive of clinically significant obstructive CAD) on the baseline study were excluded from further study participation. Rest and postexercise left ventricular ejection fraction were calculated from gated myocardial perfusion images using commercially available software (Corridor4DM; INVIA Medical Imaging Solutions, Ann Arbor, MI).

Absolute left ventricular (LV) MBF (in mL/g per minute) was computed from the dynamic rest and exercise-stress imaging series using the same commercially available software and previously validated methods.[23] Automated regions of interest were used to generate blood pool (arterial input function) and tissue time–activity curves. Regional and global LV rest and exercise MBF were calculated by fitting the ^{13}N-ammonia time–activity curves to a 2-compartment tracer kinetic model as described previously.[24,25] Per-patient global coronary flow reserve (CFR) was calculated as the ratio of absolute MBF at stress over rest for the entire left ventricle. Quantitation of MBF was performed by 2 operators blinded to the patient, treatment, and treatment order. The intraclass correlation coefficient for MBF and CFR among these readers was 0.94 (95% CI 0.88–0.98), indicating excellent reproducibility.[23] To account for differences in resting cardiac workload, which can affect global rest LV MBF, "corrected" CFR was calculated: corrected CFR=peak global LV MBF/[(rest MBF/rest rate-pressure product)×10 000].

Assessment of Diastolic and Systolic Left Ventricular Function

Resting echocardiograms were acquired by an experienced sonographer using a Philip iE33 machine (Philips Corporation, Andover, MA) and included standard 2-dimensional views recommended by the American Society of Echocardiography.[26] Acquired images were digitally stored for quantitative measurements performed by 4 expert echocardiographers blinded to the patient, treatment, and treatment order. LV end-diastolic and end-systolic volumes (used to calculate left ventricular ejection fraction), left atrial volume, septal and lateral peak early diastolic tissue velocity (e′), septal and lateral peak systolic tissue velocity (s′), and mitral inflow velocity (E) were all measured in accordance with American Society of Echocardiography guidelines.[27,28] Each measurement was performed in triplicate by the same echocardiographer for all study patients. Intraclass correlation coefficients for all echocardiographic measurements, performed on 15 randomly selected study echocardiograms, are provided in Table S1.

Statistical Analysis

We calculated that a sample size of 35 evaluable patients was needed to provide 80% power to detect a 20% relative improvement in immediate postexercise global LV CFR (primary end point) from baseline. Percent improvement from baseline in all other quantitative serum biomarker and echocardiographic measures were secondary end points. All patients who received at least 1 dose of each intervention and had a PET interpretable for CFR at all 3 study visits were included in the efficacy analysis. For the primary end point, and all secondary end points, individual multilevel mixed-effects linear regression models were used to determine independent treatment effects. In each model, percent change from baseline was used as the outcome variable and fixed effects included treatment phase (ie, ranolazine or placebo), treatment order (ie, ranolazine-first or placebo-first), and average daily dose. A per-patient random effect was included to account for any within-patient correlation of repeated measures. All statistical tests were performed with 2-sided α=0.05 and were performed using Stata software version 13.1 (StataCorp, College Station, TX).

Study Oversight

The study was investigator initiated and funded by Gilead Sciences, Inc, the American College of Cardiology, and the National Heart, Lung, and Blood Institute at the National Institutes of Health. The authors are solely responsible for the study design and conduct, all statistical analyses, drafting and editing of the manuscript, and its final contents. Study characteristics conform to the Consolidated Standards of Reporting Trials (CONSORT) guidelines for reporting randomized clinical trials. An independent Data and Safety Monitoring Board monitored patient safety.

Results

Cohort Characteristics at Baseline

From July 2013 through April 2015, 47 patients who met the inclusion and exclusion criteria were enrolled. There was 1 screen failure (obstructive CAD identified on coronary CT angiography) and 6 patients withdrew consent before randomization (Figure 1). Of the remaining 40 randomized patients, 3 dropped out while receiving ranolazine, 1 dropped out while receiving placebo, and 1 was excluded for PET images that were not interpretable for CFR. Accordingly, 35 patients were included in the primary analysis.

The baseline demographic and clinical characteristics of the study cohort are shown in Table 1. The median age was 64 years (interquartile interval [IQI]: 61–67) and 49% were women. The median baseline hemoglobin A1c was 7.4% (IQI: 6.8–8.2). Of the 19 patients (54%) with known CAD, 15 had undergone coronary revascularization (43% of the overall cohort). With respect to baseline antianginal medication use in the study cohort, 20% of patients were on long-acting nitrates, 63% were on β-blockers, and 26% were on calcium channel-blockers.

Hemodynamic Parameters at Rest and During Exercise

Compared with placebo, ranolazine treatment did not change resting heart rate, systolic blood pressure, mean arterial blood pressure, or rate–pressure product. Likewise, ranolazine treatment did not change immediate postexercise heart rate, systolic blood pressure, mean arterial blood pressure, or rate–pressure product. Cardiac workload achieved with exercise, assessed by both total metabolic equivalents and peak:rest rate–pressure product, was not significantly different between ranolazine and placebo treatments. A summary of all rest and exercise hemodynamic parameters is provided in Table S2. Importantly, our immediate postexercise hemodynamic measurements represented a drop-off of 10% or less from those at peak exercise, as shown in Table S3.

Effect of Ranolazine on Myocardial Blood Flow, Coronary Flow Reserve, Diastolic Function, and Serum Biomarkers

In multivariable analysis accounting for treatment phase, treatment order, and average daily dose, ranolazine treatment

Table 1. Study Cohort Baseline Demographic and Clinical Characteristics

	All Study Participants (n=35)
Age, y	64 [61, 67]
Female	17 (49%)
Body mass index, kg/m^2	31 [27, 36]
Cardiovascular risk factors	
Hypertension	30 (86%)
Dyslipidemia	33 (94%)
Family history of CAD	11 (31%)
Chronic kidney disease	3 (9%)
Current tobacco use	2 (6%)
Cardiovascular history	
Known CAD	19 (54%)
Myocardial infarction	6 (17%)
Coronary revascularization	15 (43%)
Percutaneous coronary intervention	8 (23%)
Coronary artery bypass grafting	10 (29%)
Stroke	2 (6%)
Peripheral vascular disease	3 (9%)
Medications	
Insulin	13 (37%)
Aspirin	28 (80%)
β-Blocker	22 (63%)
Calcium channel blocker	9 (26%)
ACE inhibitor or ARB	27 (77%)
Statin	34 (97%)
Diuretic	15 (43%)
Nitrate	7 (20%)
Symptoms	
Angina and dyspnea on exertion	24 (69%)
Angina only	8 (23%)
Dyspnea on exertion only	3 (9%)
Serum labs	
Creatinine, mg/dL	0.9 [0.7, 1.1]

Continuous variables represented as median [interquartile interval] and dichotomous variables as n (%). Symptoms were assessed by the Seattle Angina Questionnaire and the Rose Dyspnea Scale. ACE indicates angiotensin-converting enzyme; ARB, angiotensin II receptor blocker; CAD, coronary artery disease.

did not significantly alter rest or immediate postexercise global LV MBF, CFR, or corrected CFR relative to placebo (Table 2). However, in exploratory secondary analyses, we found a significant inverse correlation whereby patients with lower baseline corrected CFR were more likely to experience improvement following treatment with ranolazine (r=−0.401, P=0.02). A similar statistically significant negative correlation was not seen following treatment with placebo (r=−0.188, P=0.28) (Figure 2), though the difference between the correlation coefficients for ranolazine and placebo did not reach statistical significance (2-tailed P=0.35 utilizing the above correlation r values and n=35 for each treatment group).

In multivariable analysis accounting for treatment phase, treatment order, and average daily dose, ranolazine was associated with an improvement in E/septal e′ (P=0.001) and E/lateral e′ (P=0.01) relative to placebo (Table 2). In exploratory secondary analyses, we did not find a significant inverse correlation between baseline E/e′ (septal or lateral) and its improvement following treatment with ranolazine. Relative to placebo, ranolazine treatment did not significantly alter other echocardiographic parameters of resting systolic and diastolic cardiac performance, nor serum high-sensitivity C-reactive protein or serum N-terminal pro-B-type natriuretic peptide (Table 2).

Compliance and Safety

The median daily dose of ranolazine was 1750 mg (IQI: 1722–2000) and the median daily dose of placebo was 1750 mg (IQI: 1467–2000). There were no serious adverse events during the ranolazine or washout periods. One serious adverse event occurred during the placebo period (fall complicated by nonfatal intracerebral hemorrhage). Nonserious adverse events during the ranolazine period occurred in 12 patients (nausea and dizziness [9], hypoglycemia [1], renal abnormality [1], transaminitis [1]). Among the 12 patients with nonserious adverse events during ranolazine treatment, 3 patients dropped out of the study and in the remaining 9 patients dose reduction to 500 mg twice daily resulted in resolution of adverse effects. Nonserious adverse events during the placebo period occurred in 2 patients (hematuria [1], chest pain requiring evaluation [1]). Finally, nonserious adverse events occurred in 2 patients during follow-up after protocol completion (chest pain requiring evaluation [1], nephrolithiasis [1]). Complete follow-up at 2 weeks after protocol completion was obtained in 100% of patients.

Discussion

In our cohort of symptomatic patients with diabetes mellitus, we found that treatment with ranolazine resulted in a modest but significant improvement in diastolic function, without a change in exercise-stimulated MBF or CFR compared to placebo. In our exploratory secondary analyses, however, we found a significant inverse correlation whereby patients with lower baseline corrected CFR measurements were more likely to experience improvement following treatment with ranolazine.

Table 2. Treatment Effect of Ranolazine on MBF, CFR, Diastolic Function, and Serum Biomarkers

	Baseline Median [IQI]	Ranolazine % Change	Placebo % Change	Treatment Effect*
MBF outcomes				
Rest global MBF, mL/g per minute	0.85 [0.68, 0.95]	7 [−12, 11]	−1 [−15, 7]	*P*=0.23
Immediate postexercise global MBF, mL/g per minute	1.48 [1.23, 1.65]	3 [−14, 10]	−2 [−15, 3]	*P*=0.19
CFR	1.80 [1.43, 2.07]	0 [−10, 14]	−2 [−14, 16]	*P*=0.60
Corrected CFR†	1.50 [1.35, 1.95]	−4 [−14, 17]	2 [−17, 21]	*P*=0.84
Rest echocardiography outcomes				
Lateral e′, m/s (n=28)	0.09 [0.08, 0.10]	4 [−8, 13]	−1 [−12, 10]	*P*=0.31
Septal e′, m/s (n=28)	0.07 [0.06, 0.08]	0 [−8, 12]	−7 [−18, 10]	*P*=0.05
E/lateral e′ (n=28)	8.6 [6.6, 10.3]	−3 [−19, 14]	4 [−13, 28]	*P*=0.01
E/septal e′ (n=26)	10.2 [8.6, 11.2]	−4 [−16, 12]	8 [0, 22]	*P*=0.001
Left atrial volume, mL (n=26)	26 [22, 38]	4 [−6, 37]	11 [−19, 48]	*P*=0.21
LVEDV, mL (n=28)	77 [63, 99]	1 [−10, 7]	−2 [−15, 8]	*P*=0.04
LVESV, mL (n=28)	33 [25, 42]	−5 [−11, 27]	−2 [−22, 27]	*P*=0.20
LV ejection fraction, % (n=28)	58 [56, 63]	1 [−6, 4]	−2 [−10, 10]	*P*=0.75
Lateral s′, m/s (n=27)	0.08 [0.07, 0.09]	0 [−4, 14]	−5 [−15, 6]	*P*=0.51
Septal s′, m/s (n=28)	0.07 [0.07, 0.08]	0 [−11, 7]	−7 [−16, 5]	*P*=0.07
Serum biomarker outcomes				
Glucose, %	139 [103, 190]	6 [−12, 40]	11 [−6, 41]	*P*=0.57
Hemoglobin A1c, mg/dL	7.4 [6.8, 8.2]	−1 [−5, 4]	−2 [−6, 2]	*P*=0.96
High-sensitivity CRP, mg/L (n=31)	2.2 [1.1, 5.9]	−8 [−36, 33]	0 [−28, 25]	*P*=0.36
NT-proBNP, pg/mL (n=34)	67 [30, 113]	−10 [−36, 28]	4 [−24, 61]	*P*=0.31

CFR indicates coronary flow reserve; CRP, C-reactive protein; HR, heart rate; IQI, interquartile interval, LVEDV, left ventricular end-diastolic volume; LVESV, left ventricular end-systolic volume; MBF, myocardial blood flow; NT-proBNP, N-terminal of prohormone brain natriuretic peptide; SBP, systolic blood pressure.

*Treatment effect *P* value based on mixed linear regression model with % change from baseline as the outcome variable and fixed variables of treatment phase (ranolazine vs placebo), treatment order, and per-patient average daily ranolazine and placebo dose. A per-patient random effect was also included to account for any within-patient correlation of repeated measures.

†Corrected CFR calculation: peak global LV MBF/(rest MBF/(rest HR×rest SBP)×10 000).

Our primary observation that ranolazine does not improve CFR in symptomatic diabetic patients without obstructive CAD is concordant with the findings of Villano et al,[29] who found that ranolazine did not have an effect on coronary microvascular function in patients with microvascular angina pectoris. However, our data conflict with those of Tagliamonte et al,[17] who found that ranolazine improved CFR in patients with symptoms of myocardial ischemia in the absence of obstructive CAD. There are several possible explanations for this discrepancy. First, less than 25% of the Tagliamonte cohort had diabetes mellitus, in whom hyperglycemia and hyperinsulinemia may trigger distinct pathophysiologic mechanisms to produce microvascular ischemia compared with other disease processes.[30,31] Second, we induced coronary hyperemia with exercise while Tagliamonte et al did so with dipyridamole. Coronary hyperemia elicited with vasodilators such as dipyridamole or adenosine uncouples blood flow from cardiac work and reflects predominantly endothelial-independent vasodilation. Exercise, on the other hand, triggers a more complex interplay between metabolic demand, coronary hemodynamics, and vasodilator response. Finally, Tagliamonte et al measured CFR with echocardiography only in the left anterior descending coronary artery, whereas we measured CFR with PET over the entire LV.

Our finding that ranolazine modestly improves LV filling pressures in symptomatic diabetic patients without obstructive CAD is a novel finding. To date, the only trials examining the effect of ranolazine on echocardiographic measures of diastolic function have been in animal models or patients with heart failure with preserved ejection fraction. The data in those studies are equivocal regarding the improvement of echocardiographic measures of diastolic function with ranolazine.[32,33]

Our exploratory analyses demonstrating a potential gradient phenomenon governing the effects of ranolazine on MBF are consistent with recently published data by Bairey-Merz et al, who also showed that patients with lower baseline CFR had significantly greater improvement in midventricular

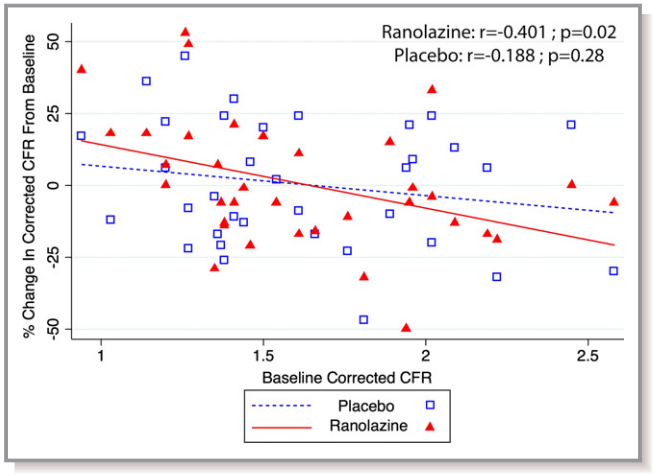

Figure 2. Correlation between baseline corrected CFR and its change after treatment with ranolazine and after treatment with placebo. CFR indicates coronary flow reserve.

myocardial perfusion reserve index with ranolazine.[34] Prior histopathologic studies in diabetic patients have shown phenotypic heterogeneity with respect to coronary arteriolar thickening, perivascular accumulations of connective tissue, and myocardial stiffening.[35,36] Patients with these phenotypic features may have more severe impairment of CFR than those with isolated endothelial dysfunction from hyperglycemia, inflammation, and oxidative stress.[30,37,38] It may be this more severe phenotype that derives more clinical benefit from treatment with ranolazine.

Finally, our protocol coupling supine bicycle exercise stress with dynamic PET imaging to quantify absolute MBF imaging is relatively novel. Krivokapich et al showed the feasibility of quantifying MBF from dynamic PET images acquired during peak exercise in normal volunteers.[39] However, the relatively longer gantry length of modern PET-CT scanners (compared to older standalone PET scanners) physically precludes supine exercise during image acquisition. Our exercise stress protocol was designed to minimize the delay between peak exercise and initiation of dynamic PET image acquisition to ≈20 s. Indeed, our baseline absolute immediate postexercise global MBF measurements (Table 2) are very similar to those measured by Krivokapich et al.[39] Accordingly, we believe this protocol may be attractive to clinical trialists seeking an accurate, precise, and reproducible noninvasive measurement of postexercise absolute MBF.

While our trial had several strengths, including a crossover trial design, a disease-focused cohort comprising both men and women, use of an exercise-based stress protocol, and well-validated imaging outcome measures, we acknowledge its limitations as well. The first is our relatively small cohort size of 35 patients, which limited generalizability and our statistical power for detecting differences in our secondary analyses and in any potential cohort subgroups. A second important limitation is that our mechanistic trial was not designed to assess clinical outcomes. Accordingly, it is possible that some of the nonsignificant improvements we saw with ranolazine compared to placebo (eg, immediate postexercise MBF, serum high-sensitivity C-reactive protein, serum N-terminal pro-B-type natriuretic peptide) could contribute to a meaningful reduction in adverse clinical outcomes in a larger population of similar patients. Finally, our experimental design allowed for inclusion of patients with nonobstructive epicardial CAD and patients with mild stress perfusion defects (summed stress score <6). While this was done to acknowledge the significant real-world challenge of identifying symptomatic diabetic patients without any epicardial coronary artery disease (ie, "pure" microvascular disease), doing so may have created a bias toward our negative CFR results. Specifically, patients in our cohort with impaired CFR more prominently influenced by diffuse "nonobstructive" epicardial atherosclerosis and/or small myocardial scarring may have been less likely to respond to any potential beneficial effects of ranolazine on microvascular function.

In conclusion, in symptomatic diabetic patients without obstructive CAD, we found that treatment with ranolazine did not change exercise-stimulated MBF or CFR but did result in a modest but significant improvement in diastolic function. In addition, our exploratory analyses suggest that diabetic patients with more severely impaired coronary flow reserve may derive more benefit from ranolazine than their counterparts with less severe phenotypes.

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Disclosures

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SUPPLEMENTAL MATERIAL

Table S1. Intraobserver and interobserver intraclass correlations for echocardiographic measurements.

	Intraclass Correlation	
Echocardiographic Measurement	**Intraobserver (n=15)**	**Interobserver (n=15)**
Lateral E', m/s	0.96	0.96
Septal E', m/s	0.94	0.49
E/lateral e'	0.99	0.97
E/septal e'	0.99	0.99
Left atrial volume, mL	0.49	0.90
LVEDV, mL	0.94	0.94
LVESV, mL	0.87	0.86
LV ejection fraction, %	0.42	0.63
Lateral S', m/s	0.93	0.83
Septal S', m/s	0.47	0.16

Two-way mixed-effects model with 2 raters and 15 targets.

Table S2. Change in rest and exercise hemodynamics, and cardiac workload achieved with exercise after treatment with placebo and ranolazine

	Baseline [IQI]	Ranolazine % Change [IQI]	Placebo % Change [IQI]	Treatment Effect*
Rest Hemodynamics				
Rest heart rate (bpm)	69 [61,77]	0 [-8,5]	0 [-11,6]	p=0.59
Rest systolic BP (mm Hg)	128 [116,137]	-4 [-8,8]	-1 [-10,12]	p=0.77
Rest MAP (mm Hg)	87 [80,92]	-3 [-10,7]	0 [-10,11]	p=0.60
Rest rate-pressure product	8806 [7442,10488]	0 [-9, 13]	-2 [-11,11]	p=0.97
Peak Exercise Hemodynamics				
Peak heart rate (bpm)	126 [118,136]	-4 [-7,0]	-2 [-7,2]	p=0.47
Peak systolic BP (mm Hg)	174 [164,186]	-3 [-8,0]	-5 [-11,3]	p=0.97
Peak MAP (mm Hg)	109 [103,121]	-3 [-8,6]	-1 [-8,5]	p=0.81
Peak rate-pressure product	22304 [20160,25944]	-6 [-14,-2]	-7 [-17,2]	p=0.51
Cardiac Workload Achieved With Exercise				
METS	5.0 [4.0,5.9]	0 [0,0]	0 [0,0]	p=0.60
Peak:rest rate-pressure product	2.6 [2.2,2.9]	-8 [-16,7]	-7 [-18,15]	p=0.74

*Treatment effect p value based on mixed linear regression model with % change from baseline as the outcome variable and fixed variables of treatment phase (ranolazine vs. placebo), treatment order, and per-patient average daily ranolazine and placebo dose. A per-patient random effect was also included to account for any within-patient correlation of repeated measures. BP, blood pressure; IQI, interquartile interval, MAP, mean arterial pressure; METS, metabolic equivalents.

Table S3. Peak exercise vs. immediate post-peak hemodynamics for all PET studies.

	Peak Exercise [IQI]	**Immediate Post-Peak [IQI]**
Heart rate (bpm)	126 [113,136]	113 [100,126]
Systolic BP (mm Hg)	172 [160,184]	173 [153,185]
MAP (mm Hg)	109 [101,118]	107 [97,117]
Rate-pressure product	21360 [18984,23944]	19379 [15714,22684]

BP, blood pressure; IQI, interquartile interval; MAP, mean arterial pressure.